REMARKS

Prior to entry of this paper, claims 1-8 were canceled, and claims 9-21 were pending and under examination.

Upon entry of this paper, claims 18-20 are canceled and claims 22-32 are added. Applicants reserve the right to pursue one or more continuing applications to canceled subject matter.

After entry of this paper, claims 9-17 and 21-32 are pending.

Support for Amendments

Upon entry of this paper, claims 18-20 are canceled, and claims 22-32 are added. Claim 10 is amended to replace the British spelling of "tumour" with the American spelling "tumor." Support can be found in the application as originally filed. Support for new claims 22-23 can be found throughout the specification as filed, for example at page 11, lines 3-10. Support for new claims 24-25 and 27-28 can be found on page 8, second paragraph. Support for new claim 26 can be found on page 8, line 8. Support for new claims 29, 30, 31, and 32 can be found throughout the specification as filed, for example at page 4, second paragraph, page 4, fifth paragraph, page 8, first and second paragraphs, page 10, third full paragraph, page 11, first paragraph.

No new matter is added.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 18-20 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement for the entire scope of the claims. The Office Action states that the specification is enabling for

treatment of certain specific tumors with ET-743, but "but does not enable the treatment of the vast variety of cancers within the scope of the claims" (OA, p. 2). The Office Action further states that the reference cited by Applicants (van Kersteren, Anti-Cancer Drugs, 14(7), 2003: 487-502) is "not sufficient to show that a composition comprising ET-743 is capable of generally treating cancer, which is inclusive of treating any cancer *in vivo* and *in vitro* - and even in a human" (OA, p. 2). The Office Action proceeds to argue that "[t]he claims are directed to treating cancer, which is not only inclusive of in vitro treatment but also in vivo in humans" (OA, p. 3). Finally, the Office Action argues that the instant specification "does not provide adequate disclosure to the skilled artisan on how calipers can be used to measure such a cancer" (OA, p. 3, referring to multiple myeloma). Accordingly, the Office Action maintains the position that the practice of the instant invention would require undue experimentation.

Applicants respectfully traverse the rejection. However, in order to advance prosecution, claims 18-20 are canceled. Applicants request withdrawal of the rejection as moot.

Rejection Under 35 U.S.C. § 103(a)

Claims 9-21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Donald *et al.* (Cancer Research, vol. 63, issue 18, pages 5902-5908, 2003) in view of Takahashi *et al.* (US 2004/0108086; corresponding to US 10/416,086). Upon entry of this paper, claims 18-20 are canceled and new dependent claims 22-28 are added. In addition, new independent claims 29-30 and dependent claims 31-32 are added. While new claims 22-32 are not rejected, Applicants present remarks below directed to all of the pending claims to expedite prosecution.

As an initial matter, Applicants request clarification as to the basis for the citation of Takahashi (US 2004/0108086) in the rejection under U.S.C. § 103(a). Takahashi (US

2004/0108086) published on June 10, 2004, which is after the claimed priority date of October 15, 2003 for the present application. Therefore, Applicants request clarification as to whether the Office Action is relying on the June 10, 2004 publication date of Takahashi (US 2004/0108086) or is relying on the May 10, 2002 publication date of WO 2002/36135, which is the PCT application from which Takahashi (US 2004/0108086) entered the national phase. If the Office Action is relying on the WO publication, Applicants respectfully request clarification of the record prior to possible appeal.

The Office Action argues that it would have been obvious to "take advantage of the hepatoprotective properties of indole-3-carbinol against damage caused by ET-743" (OA, p. 4), and therefore, it "would be obvious to treat, for example, melanoma, with the combination of drugs," (OA, p. 4). Applicants respectfully deny that any *prima facie* case of obviousness has been made. However, even assuming for the sake of argument that a *prima facie* case of obviousness has been made, Applicants respectfully submit that the present invention provides evidence of unexpected results which rebut any alleged *prima facie* case of obviousness. Specifically, the specification as filed teaches that in direct comparisons with other hepatoprotective compounds, indole-3-carbinol strongly protects the liver from ET-743 induced damage, while other hepatoprotective compounds have less effect or fail (Specification, page 5, last paragraph through page 6, first paragraph).

As detailed in the specification, several hepatoprotective compounds were tested for their capacity to protect the liver from ET-743 induced damage, including β-naphthoflavone, phenobarbitone, and N-acetylcysteine. The three comparison compounds are known to induce cytochrome P450 enzyme families, and thus can increase the rate of oxidative metabolic disposition of drugs (Specification, page 6, first paragraph). The specification reports that

amelioration of ET-743 mediated hepatotoxicity by β-naphthoflavone persisted only for a short term, while the effect by phenobarbitone was weak, as reflected by significant suppression of elevation of only bilirubin, but not of other biochemical indicators of hepatotoxicity. Finally, the specification reports that N-acetylcysteine failed altogether to protect livers against ET-743 induced damage (Specification, page 6, first paragraph).

Applicants also refer to Donald et al, "Comparison of four modulators of drug metabolism as protectants against the hepatotoxicity of the novel antitumor drug yondelis (ET-743) in the female rat and in hepatocytes in vitro," Cancer Chemother Pharmacol, April 2004, vol. 53, pp. 305-12; cited in the attached supplemental IDS). In the reference, it is further shown that any protection by β-naphthoflavone only persisted for a short time, any protection by phenobarbitone was weak, and N-acetylcysteine failed altogether (p. 309, right column, lines 1-7). The reference provides further evidence from the scientific literature that one of ordinary skill in the art cannot merely take any family of hepatoprotective compounds and assume that various classes of hepatoprotectors will provide a benefit when administered with ET-743.

Applicants further suggest that such results provide evidence against a reasonable expectation of success. It is an accepted principle of patent law that while absolute certainty is not necessary to establish a reasonable expectation of success, In re O'Farrell, 853 F.2d 894, 903-04, 7 USPQ2d 1673, 1681 (Fed. Cir. 1988), there can be little better evidence negating an expectation of success than actual reports of failure. See, e.g., In re Rinehart, 531 F.2d 1048, 1053-54, 189 USPQ 143, 148-49 (CCPA 1976). In this case, both the specification and the scientific literature provide reports of actual failure in reducing the hepatotoxic effects of ET-743 by administering hepatoprotectors of various classes. Thus, both the specification and the scientific literature provide evidence negating an expectation of success. Where the Office

Action argues that it would have been obvious to "take advantage of the hepatoprotective properties of indole-3-carbinol against damage caused by ET-743" (OA, p. 4), Applicants have surprisingly shown that indole-3-carbinol succeeds, where other families of hepatoprotective agents fail to exhibit hepatoprotective properties against damage caused by ET-743, providing further evidence against an expectation of success.

Moreover, there is no suggestion in the Takahashi and Donald references cited in the Office Action that the antitumor effectiveness of ET-743 can be maintained while administering indole-3-carbinol or one or more derivatives or pharmaceutically acceptable salts thereof. In the specification, Examples 2 and 3, Applicants have shown that the antitumor properties of ET-743 are not negatively affected by administration as a combination therapy with indole-3-carbinol. The assay in Example 2 was designed to demonstrate *in vivo* that indole-3-carbinol does not adversely affect the antitumor activity of ET-743. The tumor weight inhibition (TWI) results show that a combination of ET-743 with a dose of indole-3-carbinol with hepatoprotective effects (as shown in Example 1) not only maintains the antitumor properties of ET-743, but actually improves the TWI. Furthermore, the study in Example 3 was designed to determine if pre-treatment with indole-3-carbinol alters clearance of ET-743 from plasma and the liver *in vivo*. The results in Example 3 show that indole-3-carbinol does not alter ET-743 disposition in the plasma or liver markedly, consistent with its un-impeded antitumor activity.

In other words, the Takahashi and Donald references fail to provide any teaching or suggestion with regard to the antitumor properties of the combination of ET-743 and indole-3-carbinol. As such, the combination of the cited references fails to render obvious the present limitations of "effective treatment of a tumor by combination therapy" as in claims 10, 29, and 30. Moreover, the cited combination of references fails to provide any teachings with respect to